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Lenz Microphthalmia Syndrome – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Lenz microphthalmia syndrome (LMS) is characterized by unilateral or bilateral microphthalmia and/or clinical anophthalmia with malformations of the ears, teeth, fingers, skeleton, and/or genitourinary system. Microphthalmia is often accompanied by microcornea and glaucoma. Coloboma is present in approximately 60% of microphthalmic eyes with severity ranging from isolated iris coloboma to coloboma of the ciliary body, choroid, and optic disk. Ears may be low set, anteverted, posteriorly rotated, simple, cup shaped, or abnormally modeled. Hearing loss has been observed. Dental findings include irregularly shaped, missing, or widely spaced teeth. Duplicated thumbs, syndactyly, clinodactyly, camptodactyly, and microcephaly are common, as are narrow/sloping shoulders, underdeveloped clavicles, kyphoscoliosis, exaggerated lumbar lordosis, long cylindric thorax, and webbed neck. Genitourinary anomalies include hypospadias, cryptorchidism, renal hypoplasia/aplasia, and hydroureter. Approximately 60% of affected males have mild-to-severe intellectual disability or developmental delay.

Diagnosis/testing

The diagnosis of Lenz microphthalmia syndrome is based on clinical findings. Mild simple microphthalmia can be identified by measuring the axial length of the globe with A-scan ultrasonography. *NAA10* (MCOPS1 locus) and *BCOR* (MCOPS2 locus) are the only genes known to be associated with Lenz microphthalmia syndrome (LMS).

Management

Treatment of manifestations: For clinical anophthalmos or extreme microphthalmos: regular evaluation by an ocularist for placement of serial enlarging orbital expanders, physical and occupational therapy, special

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education, and referral to services for the blind. For hearing loss and sleep disorders: treatment dependent on the specific defect and similar to that used in the general population. Institute regular dental examinations and cleaning should be instituted, especially when cognitive developmental delay is present; dental treatment as for the general population.

Surveillance: Annual ophthalmologic examination for those with residual vision, monitoring of renal function, developmental assessments, and lifelong case management to help affected individuals gain access to social services and assistive devices for the blind.

Genetic counseling

Lenz microphthalmia syndrome is inherited in an X-linked manner. The risk to sibs depends on the carrier status of the mother. If the mother is a carrier, the chance of transmitting the pathogenic variant is 50% in each pregnancy: males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers. The majority of males with Lenz microphthalmia syndrome do not reproduce. Carrier testing for at-risk female relatives and prenatal testing for pregnancies at increased risk are possible for families in which the pathogenic variant has been identified in an affected family member. Prenatal ultrasound examination at 18 weeks' gestation can be offered for pregnancies at increased risk to evaluate fetal renal development.

Diagnosis

Suggestive Findings

Lenz microphthalmia syndrome (LMS) should be suspected in males with a combination of the following clinical findings:

- **Ocular malformation.** Unilateral or bilateral microphthalmia and/or anophthalmia that may be symmetric or asymmetric:
  - **Anophthalmia** refers to the histologic diagnosis of complete absence of the globe in the presence of ocular adnexae (eyelids, conjunctiva, and lacrimal apparatus). CT or MRI scan of the orbit shows absence of ocular tissue, optic nerve, and extraocular muscles. Note: The term "clinical anophthalmia" should be used for severe microphthalmia when the globe is not detectable on physical examination.
  - **"Simple microphthalmia" or "pure microphthalmia"** describes a globe that is reduced in total axial length (TAL), has all structural elements intact, and retains some vision. Mild simple microphthalmia can be identified by measuring the axial length of the globe with A-scan ultrasonography. Total axial length of the neonatal eye is normally near 17 mm; an age-adjusted total axial length below the fifth centile defines microphthalmia. The mean total axial length of the adult eye is 23.8 mm; a total axial length of less than 18.5 mm defines microphthalmia.
  - **Coloboma** is present in approximately 60% of microphthalmic eyes [Ng et al 2002], with severity ranging from isolated iris coloboma to coloboma of the ciliary body, choroid, and optic disk.
  - **Congenital cystic eye** has not been observed in LMS.
- **Extraocular malformations** that vary within and among families:
  - Hypospadias, cryptorchidism, renal aplasia/hypoplasia, hydroureter (77% of individuals)
  - Simple, anteverted, abnormally modeled ears (63%)
  - Abnormal shape of incisors, irregularly spaced teeth (48%)
  - Duplicated thumbs, syndactyly, clinodactyly, camptodactyly (44%)
  - Microcephaly (37%)
  - Narrow/sloping shoulders, underdeveloped clavicles, kyphoscoliosis, exaggerated lumbar lordosis, long cylindrical thorax, webbed neck (26%)
  - Cleft lip/palate (7%)

- **Intellectual disability** ranging from mild to severe (63%)
- **Family history** consistent with X-linked recessive inheritance

Establishing the Diagnosis

The diagnosis of LMS is established in a proband with identification of a pathogenic variant in one of two known genes, *BCOR* or *NAA10* (see Table 1).

One genetic testing strategy is serial single-gene molecular genetic testing of *BCOR* and *NAA10*.

- ***BCOR.*** p.Pro85Leu, the only *BCOR* pathogenic variant found in individuals with LMS to date, can be identified by targeted analysis for pathogenic variants [Ng et al 2004, Hilton et al 2009, Suzumori et al 2013]. If targeted analysis does not identify a pathogenic variant, sequence analysis can be performed, followed by deletion/duplication analysis if no pathogenic variant is identified.
- ***NAA10.*** c.471+2T>A is to date the only *NAA10* pathogenic variant (found in 1 family with LMS). Sequencing of *NAA10* should be performed first. If no pathogenic variant is identified, deletion/duplication analysis for partial or complete *NAA10* deletion should be considered.

An alternative genetic testing strategy is use of a multigene panel that includes *BCOR, NAA10* and other genes of interest (see Differential Diagnosis). Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

More comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of LMS.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Lenz Microphthalmia Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant Detectable by Method	
		Affected Males	Carrier Females
BCOR	Targeted sequence analysis for c.254C>T [2, 3]	Unknown [3]	Unknown [3]
NAA10	Sequence analysis [4]	Unknown [5]	Unknown [5]
	Deletion/duplication analysis [6]	Unknown	Unknown

Table 1. continued from previous page.

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant Detectable by Method	
		Affected Males	Carrier Females
Unknown [7]	NA		

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants detected in this gene.
2. Pathogenic variants included in a panel may vary by laboratory.
3. A pathogenic missense variant, c.254C>T, resulting in a change of amino acid at position 85 from proline to leucine (p.Pro85Leu) in *BCOR*, was found in affected males of the family used to map the MOCPS2 locus [Ng et al 2002, Ng et al 2004], in a white male reported by Hilton et al [2009], and in two Japanese families reported by Suzumori et al [2013]. The low frequency of *BCOR* pathogenic variants does not allow determination of the variant detection frequency.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. c.471+2T>A, a splice variant that may lead to aberrant splicing of exons 7 and 8 of *NAA10*, has been reported in three affected males with the LMS phenotype that mapped to the MCOPS1 locus [Forrester et al 2001, Esmailpour et al 2014]. The frequency of *NAA10*-associated LMS is unknown.
6. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may inlcude quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
7. An Irish family with microphthalmia/anophthalmia, ankyloblepharon and intellectual disability (MCOPS4) was previously mapped to Xq27-q28 [Graham et al 1991]. No causative gene has been identified (one individual from this family was screened for an *NAA10* pathogenic variant and none was found [Esmailpour et al 2014].

Clinical Characteristics

Clinical Description

The phenotype of Lenz microphthalmia syndrome, microphthalmia with developmental delay and skeletal and urogenital anomalies associated with *NAA10* (MCOPS1 locus) cannot easily be distinguished from the LMS phenotype caused by the pathogenic missense variant p.Pro85Leu in *BCOR* (MCOPS2 locus). It is difficult to make phenotypic comparisons between MCOPS1 and MCOPS2 as only one family has been identified with an *NAA10* pathogenic variant. Affected males with *NAA10* splice variant c.471+2T>A exhibited a greater degree of cognitive impairment, gastrointestinal symptoms, two-three toe cutaneous syndactyly with short terminal phalanges in the hand, and development of scoliosis and neuropathic muscle degeneration over time. These findings have not been reported in males with LMS caused by the *BCOR* variant p.Pro85Leu.

Lenz microphthalmia syndrome has a wide spectrum of ocular and extraocular abnormalities.

Eyes. The eyes may be asymmetrically affected. One globe can be of normal size while the other is microphthalmic. Severity can range from mild microphthalmia with retained vision to severe microphthalmia or clinical anophthalmia with blindness. Microphthalmia is often accompanied by microcornea and reduction in the size of the anterior segment of the eye, which predispose to the development of glaucoma.

Since mild microphthalmia may not be obvious on clinical examination, individuals with LMS with retained vision may not be identified until the first ophthalmologic examination when high hyperopia (+7 to +11 diopters) secondary to a foreshortened posterior segment of the globe is diagnosed.

Cataracts may be present.

Nystagmus may be present secondary to impaired vision.

Absence or diminished size of the globe may cause secondary underdevelopment of the bony orbits, shortened palpebral fissures, and fusion of the eyelid margins (ankyloblepharon).

Craniofacial. The occurrence of congenital microcephaly is variable. Affected individuals may be normocephalic or dolichocephalic.

Ears may be low set, anteverted, posteriorly rotated, simple, cup shaped, or abnormally modeled. Preauricular tags may be present.

Hearing loss has been observed.

Cleft lip/palate or high arched palate is present in approximately 12/30 of individuals [Ng et al 2002].

Dental development may be delayed. Nonspecific dental findings include irregularly shaped, missing, or widely spaced teeth.

Genitourinary. Urogenital anomalies are the most frequent associated findings, reported in approximately 23/30 of individuals [Ng et al 2002]. These include hypospadias, cryptorchidism, renal hypoplasia/aplasia, and hydroureter.

Limbs. Hand findings include duplicated and/or proximally placed thumbs, cutaneous syndactyly, clinodactyly, and camptodactyly.

Skeletal. Long cylindric thorax with sloping, narrow shoulders, underdeveloped clavicles, or thinning of the lateral third of the clavicles on x-ray as well as kyphoscoliosis and exaggerated lumbar lordosis have been seen in some families.

Cognitive/neurologic. Cognitive impairment varies within and among families. Approximately 22/35 of affected males have mild-to-severe intellectual disability or developmental delay [Ng et al 2002].

Motor development may be delayed.

Seizures, behavioral disturbance, and self-mutilation may manifest in males with severe intellectual disability. Sleep-wake cycles can be disturbed because of lack of normal diurnal variation.

Cranial MRI often reveals absent or hypoplastic optic nerves and optic chiasm. In addition, hypoplasia of the corpus callosum and cingulate gyrus has been noted. The latter is often clinically silent.

Heterozygotes. Features of LMS and OFCD have not been reported in female carriers of the *BCOR* variant p.Pro85Leu. In one family, two-three toe cutaneous syndactyly and short terminal phalanges in the hand were reported in female carriers of *NAA10* variant c.471+2T>A [Esmailpour et al 2014].

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Males reported with LMS and a *BCOR* pathogenic variant had the p.Pro85Leu pathogenic variant; however, one reported male exhibited radioulnar synostosis, which occurs in 7/35 of those with oculofaciocardiodental (OFCD) syndrome (see Genetically Related Disorders). Thus, the presence of radioulnar synostosis in a male with LMS may indicate the presence of a *BCOR* pathogenic variant [Hilton et al 2009].

Penetrance

An insufficient number of cases of Lenz microphthalmia exist to comment on penetrance.

Nomenclature

Lenz microphthalmia syndrome (LMS) has been referred to as Lenz dysplasia, Lenz dysmorphogenetic syndrome, and microphthalmia with associated anomalies. The two loci were formerly designated MAA and MAA2 (or ANOP2).

The locus designations MAA (now associated with syndromic microphthalmia 1 [MCOPS1, *NAA10*]), and MAA2 (now associated with syndromic microphthalmia 2 [MCOPS2, *BCOR*]) were used to highlight the genetic heterogeneity of LMS and the associated extraocular developmental anomalies and intellectual disability that co-occur with the microphthalmia in affected males.

MCOPS2 has since been redesignated oculofaciocardiodental syndrome (OFCD) due to the higher prevalence of *BCOR* loss-of-function variants with OFCD. However, the *BCOR* p.Pro85Leu pathogenic missense variant remains a known cause of LMS.

Although the consensus inheritance pattern is X-linked recessive, the term Lenz microphthalmia is used by clinicians for simplex cases (i.e., single occurrence in a family) with a Lenz-like phenotype.

Prevalence

Prevalence in ethnic groups is unknown. Most reported cases are of European descent. *BCOR* p.Pro85Leu appears to be pan ethnic and has been reported in an African American family [Ng et al 2002], a European family [Hilton et al 2009], and two Japanese families [Suzumori et al 2013]. *NAA10* c.471+2T>A has been found in one family of mixed European descent [Esmailpour et al 2014].

Genetically Related (Allelic) Disorders

Oculofaciocardiodental (OFCD) syndrome is also associated with pathogenic variants in *BCOR* [Ng et al 2004, Horn et al 2005, Oberoi et al 2005].

OFCD syndrome is inherited in an X-linked pattern with male lethality.

Females with OFCD syndrome may have congenital cataracts as the sole ocular manifestation or unilateral/bilateral microphthalmia with congenital cataracts. Microphthalmia is less severe in OFCD syndrome than in LMS.

Extraocular features include long narrow face, broad nasal tip with separated nasal cartilage, cleft palate, submucous cleft palate, cardiac anomalies (ventricular septal defect, atrial septal defect, floppy mitral valve) and dental anomalies (retained deciduous teeth, canine radiculomegaly, root dilacerations, oligodontia).

Females with OFCD syndrome have normal intelligence, in contrast to males with LMS, who often have developmental delay/intellectual disability, microcephaly, and structural CNS abnormalities.

The majority of individuals with OFCD syndrome analyzed thus far have detectable *BCOR* pathogenic variants [Ng et al 2004, Horn et al 2005, Hilton et al 2009]. Two *BCOR* deletions that encompass several exons have been observed and can be detected by targeted array CGH.

Individuals with OFCD syndrome have pathogenic variants that are predicted to prematurely truncate the BCOR protein. In hemizygous males, truncating variants are hypothesized to lead to a complete loss of *BCOR* function and are presumed to be lethal. Truncating *BCOR* variants in females lead to haploinsufficiency and a milder phenotype. All families with OFCD syndrome have unique pathogenic variants.

Based on the known cases of OFCD syndrome scanned for *BCOR* pathogenic variants, penetrance is complete.

Three females with features of OFCD syndrome but with notable absence of dental radiculomegaly did not have identifiable *BCOR* pathogenic variants [Hilton et al 2009].

Ogden syndrome is also associated with *NAA10* pathogenic missense variants (p.Ser37Pro and p.Arg116Trp) [Rope et al 2011]. Ogden syndrome is an X-linked disorder with male lethality during infancy. Affected males have multiple dysmorphic features (prominent eyes, downslanting palpebral fissures, large ears, and microretrognathia), congenital heart defects, delayed closure of fontanelles, scoliosis, cutis laxa, neurologic abnormalities (seizures and hypotonia) and cardiac arrhythmia. Female carriers of these pathogenic missense variants are asymptomatic.

Differential Diagnosis

A Hispanic family with isolated X-linked colobomatous microphthalmia has been reported [Lehman et al 2001] and an American family of European descent with syndromic X-linked colobomatous microphthalmia has been identified with a frameshift variant in *HMGB3* [Scott et al 2014].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Lenz microphthalmia syndrome (LMS), the following evaluations are recommended:

- Physical examination for the presence of anomalies associated with the disorder
- Cranial MRI to estimate the size of the globes for prognosis regarding potential visual function and to detect concurrent CNS malformations such as hypoplastic corpus callosum and cingulate gyrus
- Visual evoked response testing and ophthalmologic examination to help determine visual acuity and/or the potential for vision
- Consideration of echocardiogram if physical exam detects findings suggestive of a congenital cardiac malformation. (A single case report from Japan described an infant with a molecularly confirmed LMS (BCOR p.Pro85Leu) dying of an unspecified cardiac defect at age six months [Suzumori et al 2013].)
- Renal ultrasound examination to evaluate for renal aplasia, hypoplasia, and hydroureter
- Consideration of hearing evaluation during infancy if:
  - Head and neck examination reveals malformations of the auricle or ear canal, presence of skin tags or dimples around the ear, presence of cleft lip or palate, asymmetric facies, and microcephaly
  - The parents have concerns that the child cannot hear (e.g., infant does not startle to loud noises, awaken to sound). The type of examination should be adjusted for the individual's cognitive level to allow for cooperation and maximize the chance of an informative test (see Deafness and Hereditary Hearing Loss Overview).
- Consideration of sleep evaluation if parents report excessive daytime somnolence, altered sleep-wake cycles, difficulty awakening the child or getting the child to fall asleep, apnea, loud snoring, and/or difficulty breathing while asleep
- Clinical genetics consultation

Treatment of Manifestations

Individuals with anophthalmos or extreme microphthalmos benefit from regular evaluations by an ocularist for placement of serial enlarging orbital expanders to prevent deformation of facial structures and to encourage normal development of eye lashes and lid margins.

Early intervention with physical therapy and occupational therapy helps to address disturbances of the sleep-wake cycle caused by lack of light perception and problems of delayed gross motor development often observed in children with visual impairment.

Early intervention with special education maximizes cognitive development.

Referral to services for the visually impaired is recommended.

Treatment for hearing loss and sleep disorders is dependent on the specific defect and similar to the general population.

Referral to a sleep disorder specialist may be necessary depending on the individual's history and presentation to determine the appropriate tests.

Dental examinations and cleaning should be instituted to monitor dental hygiene, especially when the affected individual has cognitive developmental delay. Missing and irregularly shaped teeth and wide spacing of teeth are common. Treatment is the same as for the general population in restoring masticatory function.

Prevention of Secondary Complications

No special preventative care is recommended. Follow-up care is personalized based on the physical impairments found in the individual.

Surveillance

The following are appropriate:

- Annual ophthalmologic examination for those with residual vision given the predisposition to glaucoma and high hyperopia from foreshortening of the globe
- Monitoring of renal function (BUN, creatinine, and urine analysis) in those with known renal/ureteral anomalies
- Developmental assessments performed with each well-child visit as recommended by the American Academy of Pediatrics. More frequent and specialized assessments are tailored to each child if development is not on track.
- Lifelong case management to help affected individuals gain access to social services and assistive devices for the blind

Agents/Circumstances to Avoid

In those with residual vision, dilating drops and medications that may dilate the pupils (i.e., antihistamines, decongestants, tricyclic antidepressants) should be used in consultation with an ophthalmologist because of the narrow anterior chamber and risk for angle closure glaucoma.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Lenz microphthalmia syndrome is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will neither have the disease nor be a carrier of a *BCOR* or *NAA10* pathogenic variant.
- In a family with more than one affected male, the mother of an affected male is an obligate carrier.
- If only one male in the family is affected, the mother may be a carrier or the affected male may have a *de novo* pathogenic variant, in which case the mother is not a carrier. The frequency of *de novo* pathogenic variants is not known. To date, all published cases have been inherited.
- To date there are no reports of germline mosaicism in a mother.

Sibs of a proband. The risk to sibs depends on the carrier status of the mother:

- If the mother of the proband has a *BCOR* or *NAA10* pathogenic variant, the chance of transmitting the pathogenic variant in each pregnancy is 50%. Male sibs who inherit the pathogenic variant will be affected; female sibs who inherit the pathogenic variant will be carriers.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. The majority of males with Lenz microphthalmia syndrome do not have children, possibly as a result of infertility or decreased reproductive fitness secondary to cognitive impairment. Males who are capable of reproducing pass the pathogenic variant to all of their daughters and none of their sons.

Other family members. The proband's maternal aunts may be at risk of being carriers and the aunts' offspring, depending on their gender, may be at risk of being carriers or of being affected.

Carrier Detection

Carrier testing for at-risk females requires prior identification of the *BCOR* or *NAA10* pathogenic variant in the family.

Note: Carriers are heterozygous for this X-linked disorder and are generally asymptomatic (see Clinical Description, **Heterozygotes**).

Related Genetic Counseling Issues

Family planning

- The optimal time for discussion of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *BCOR* or *NAA10* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for Lenz microphthalmia syndrome are possible.

Ultrasound examination. Prenatal ultrasound examination at 18 weeks' gestation can be offered for pregnancies at increased risk to evaluate fetal renal development. No data exist regarding the effectiveness of screening for other malformations in fetuses at risk for LMS, although prenatal ultrasound at 15 weeks' gestation found evidence of unopened palpebral fissures suggestive of underdeveloped eyes [Suzumori et al 2013].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Lenz microphthalmia
- **International Children's Anophthalmia and Microphthalmia Network (ICAN)**
  c/o Center for Developmental Medicine and Genetics
  5501 Old York Road
  Genetics, Levy 2 West
  Philadelphia PA 19141
  Phone: 800-580-4226 (toll-free)
  Email: ican@anophthalmia.org
  www.anophthalmia.org
- **National Eye Institute**
  31 Center Drive
  MSC 2510
  Bethesda MD 20892-2510
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **National Federation of the Blind (NFB)**
  200 East Wells Street
  (at Jernigan Place)
  Baltimore MD 21230
  Phone: 410-659-9314
  Fax: 410-685-5653
  Email: pmaurer@nfb.org
  www.nfb.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Lenz Microphthalmia Syndrome: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MCOPS1	*NAA10*	Xq28	N-alpha-acetyltransferase 10	NAA10 @ LOVD	NAA10	NAA10
MCOPS2	*BCOR*	Xp11.4	BCL-6 corepressor	BCOR @ LOVD	BCOR	BCOR

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Lenz Microphthalmia Syndrome (View All in OMIM)

300013	N-ALPHA-ACETYLTRANSFERASE 10, NatA CATALYTIC SUBUNIT; NAA10
300485	BCL6 COREPRESSOR; BCOR
309800	MICROPHTHALMIA, SYNDROMIC 1; MCOPS1

BCOR

Gene structure. *BCOR* extends over approximately 55 kb and includes 15 exons. The reference cDNA for *BCOR* isoform 1 is 6182 bp (NM_017745.5). The open reading frame is 5163 bp. *BCOR* isoform 2 is 3676 bp. *BCOR* long isoform, alternatively spliced is 5810 bp (AY316592.1). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Four families have been reported with males affected with Lenz microphthalmia syndrome (LMS) due to (MCOPS2) c.254C>T (p.Pro85Leu) [Ng et al 2004, Hilton et al 2009, Suzumori et al 2013].

Table 2. *BCOR* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.254C>T	p.Pro85Leu	NM_017745.5 NP_060215.4

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *BCOR* isoform 1 encodes a protein of 1721amino acids. *BCOR* isoform 2 encodes a protein of 1004 amino acids. *BCOR* long isoform, alternatively spliced encodes a protein of 1755 amino acids.

Abnormal gene product. The p.Pro85Leu pathogenic variant is expressed and results in perturbation of ocular and extraocular organ development. Truncated and abnormally spiced variants of *BCOR* have not been detected in individuals with OFCD syndrome and are hypothesized to be eliminated by nonsense-mediated mRNA decay.

NAA10

Gene structure. *NAA10* isoform 1 encodes a protein consisting of 235 amino acids. *NAA10* isoform 2 encodes a protein consisting of 220 amino acids and isoform 3 encodes a protein of 229 amino acids. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The c.471+2T>A pathogenic variant affects the *NAA10* canonical splice donor site of intron 7. Primers amplifying the *NAA10* cDNA of exons 5 through 8 showed the presence of an abnormal exon7-intron7-exon8 fusion product (mutated splice variant 1) and no wild-type cDNA product was present in affected males [Esmailpour et al 2014].

Table 3. *NAA10* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.471+2T>A	Unknown	NM_003491.3 NP_003482.1

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *NAA10* codes for the catalytic subunit of the N-terminal acetyl transferase (hNatA) [Starheim et al 2009, Rope et al 2011]. N-terminal acetylation (NAT) of proteins is one of the most common protein modifications [Arnesen 2009]. It is estimated that hNatA has over 8000 human protein substrates [Starheim et al 2009]; hNatA complex is highly conserved from yeast. Knockdown experiments of hNatA affected substrates involved in protein-protein interactions, transcriptional regulation, ribosome assembly, RNA maturation, and protein folding and modification [Starheim et al 2009].

Abnormal gene product. A lower molecular weight protein compared to wild-type control was present in one affected male suggesting the presence of a truncated NAA10 protein; protein sequencing was not performed. Fibroblasts derived from affected males showed deficient growth compared to normal control. Western blot analysis of fibroblast derived protein from an affected male showed no detectable wild-type NAA10 protein [Esmailpour et al 2014]. Results from gene expression profile from three affected males suggested perturbation of the retinoic signaling pathway [Esmailpour et al 2014].

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Chapter Notes

Revision History

- 7 November 2019 (ma) Chapter retired: extremely rare
- 2 October 2014 (me) Comprehensive update posted live
- 29 April 2010 (me) Comprehensive update posted live
- 27 July 2007 (cd) Revision: clinical testing for *BCOR* mutations no longer available
- 6 September 2006 (cd) Revision: FISH, mutation scanning, linkage analysis, and X-chromosome inactivation studies no longer clinically available for *BCOR*
- 23 June 2006 (ca) Comprehensive update posted live
- 12 April 2005 (dn) Revision: *BCOR* testing clinically available
- 13 May 2004 (me) Comprehensive update posted live
- 5 February 2004 (dn) Revision: Molecular Genetics
- 4 June 2002 (me) Review posted live
- 8 February 2002 (dn) Original submission

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